the claimed subject matter, but rather simply to refine the description of what was covered by the claims in the originally filed form. Support for these amendments are found throughout the specification and in the originally filed claims.

These amendments raise no new issues and the Applicants respectfully request that they be entered.

Claim Objections:

In accordance with 37 C.F.R. §1.126, the claims are now renumbered consecutively beginning with the next number following the highest number claim of the previously presented claim. Also, dependencies of claims 38-55 have been altered to provide appropriate dependencies and accordingly, Applicants submit that claims 36-55 are now drawn to the presently elected invention.

Rejections Under 35 U.S.C.§103(a)

Claims 36 and 37 are rejected under 35 U.S.C.§103(a) being as unpatentable over Heller et al.(Heller), in view of Wiles et al. (Wiles). Applicants respectfully disagree.

Heller discloses a microelectronic device comprising microelectrodes that detect molecular interactions between oligonucleotide probes and a target nucleic acid molecule. However, Heller does not teach or suggest electrochemical detection methods. Instead, it teaches fluorescent and optical detection.

Wiles teaches methods of producing an improved reference electrode, and preferably teaches a silver/silver tetraphenylborate (TPB) reference electrode. Wiles also recites candidate ions, including lithium, for use in a permselective ion reference electrode. Wiles uses lithium to improve the performance of the reference electrode, not for electrochemical detection of nucleic acids or proteins.

In contrast, the current invention teaches measuring molecular interactions between nucleic acids or peptides using electrochemical detection, and uses systems that do not require electrochemical reporter moieties. Instead, the current invention utilizes lithium ions from the electrolyte to provide an electrochemical signal.

As the Examiner is aware, the test for obviousness is whether the claimed invention as a whole would have been obvious at the time it was made to a person of ordinary skill in the art. A *prima facie* case of obviousness requires that there must be some suggestion or motivation, either in the references or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings and that the prior art references must teach or suggest all the claim limitations. See M.P.E.P. § 2142.

The Examiner says that it would be obvious to one of skill in the art to use lithium taught by Wiles in the electrode of Heller and cites col.4, last paragraph of Wiles as the motivation for the combination of Heller and Wiles. However, the Applicants respectfully point out that this statement is taken out of context. The referenced paragraph refers to the use of Wiles' electrodes as reference electrodes for biological moiety sensing.

Accordingly, the Examiner has failed to point to any teaching in any of the cited references that would have motivated one of ordinary skill in the art to combine these references. Neither Heller nor Wiles suggests the desirability of such a combination. Applicants respectfully remind the Examiner that "[t]he mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills,* 16 USPQ2d 1430 (Fed. Cir. 1990); M.P.E.P. § 2143.01. Absent evidence of explicit motivation to combine the references, Applicants submit that the Examiner has failed to establish a *prima facie* case of obviousness.

Furthermore, even if, *arguendo*, the above cited references were combined, they still do not teach all the claim limitations in claims 36 and 37. Heller does not teach electrochemical detection of molecular interactions or the use of lithium. Wiles neither explicitly nor implicitly teaches use of lithium in an electrolyte buffer for electrochemical detection of nucleic acids or proteins. The combination of Heller and Wiles may have, at most, resulted in the use of a lithium electrode for detecting molecular interactions using Heller's optical or fluorescent detection systems.

Accordingly, the Applicants submit that claims 36 and 37 are not obvious over Heller and Wiles. Hence, Applicants believe that every issue under Section 103(a) has been addressed, and respectfully request the withdrawal of these rejections.

On the basis of the amendments and remarks presented herein, Applicants believe that this application is now in condition for immediate allowance. Applicants respectfully request

that the Examiner pass this application to issue and an early notice of such is requested.

Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Dated: 8/3/01

Robin M. Silva (38,304)

Four Embarcadero Center, Suite 3400
San Francisco, CA 94111-4187
Telephone: (415) 781-1989
1051205